

CROSS-REFERNCE TO RELATED APPLICATION

This is a CIP application of U.S. patent application Ser. No. 10/039,557 filed on 01/08/2002 , and for which priority is claimed under 35 U.S.C..sctn.120.

AMINOTHIOL COMPOUND

BACKGROUND OF THE INVENTION

1. Field of the Invention

5 The present invention relates aminothiol compounds which perform as superior catalysts in the asymmetric addition reactions of organic zinc and aldehyde.

2. Description of the Related Technology

10 For preparing secondary alcohols, one of the most important methods is to react organic zinc with aldehyde in addition reactions. In order to accelerate this reaction, chiral aminoalcohols are usually added as ligands to combine with organic zinc. Such chiral aminoalcohol create an asymmetric reaction environment, so that one of the produced chiral
15 secondary alcohols is produced more than its stereoisomer, i.e., the asymmetric addition reactions. Apparently, the crux of obtaining a high chemical yield as well as enantioselectivity in the above reactions is to select proper chiral compounds which can provide excellent asymmetric environment for catalytical process.

20 Though many chiral compounds used in the addition reactions regarding organic zinc and aldehyde can achieve good enantioselectivity, however, these compounds have to be added at an amount at least 1% of the main reactants, and usually around 20%. Additionally, the enantioselectivity always decays with decreasing amount of the chiral
25 ligands used. In general, the enantioselectivity is reduced below 90% enantiomeric excess (e.e.) when the chiral ligands are descended under 5%, so that most of above reactions are not good enough for industrial usage.

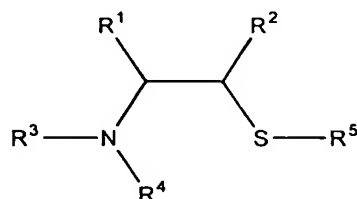
30 Aminoalcohols with optical activity, such as N,N-dibutylnorephedrine, are frequently applied to accelerating the asymmetric addition reactions of organic zinc and aldehyde as chiral ligand catalysts. By adding aminoalcohols, enantioselectivity of the above reactions can be reached as high as 99% e. e., but an amount 10-20% of chiral aminoalcohols is need. Therefore, it's an important issue how to reduce

the necessary amount of the chiral ligands used in the catalysis, so that it can be an economically efficient process

SUMMARY OF THE INVENTION

The object of the present invention is to provide aminothiols with two chiral centers, which can increase enantioselectivity of asymmetric addition of organic zinc and aldehyde.

In order to achieve the above object, the present invention discloses an aminothiol compound having a general formula I;

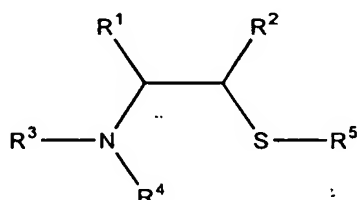


wherein R¹-R⁵ are substitutable ligands.

According to the present invention, the aminothiol compounds can perform as superior catalysts in asymmetric addition reactions wherein organic zinc and aldehyde are involved. In such reactions, though the catalysts are added only 0.1% or even 0.02%, enantioselectivity higher than 98% e.e. can always be obtained. Such catalyses are economically useful for industries.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the present invention, aminothiol compounds have a general formula I,



wherein R^1 is aryl or alkyl of C1-C9;

R^2 is aryl or alkyl of C1-C9;

R^3 is aryl or alkyl of C1-C9;

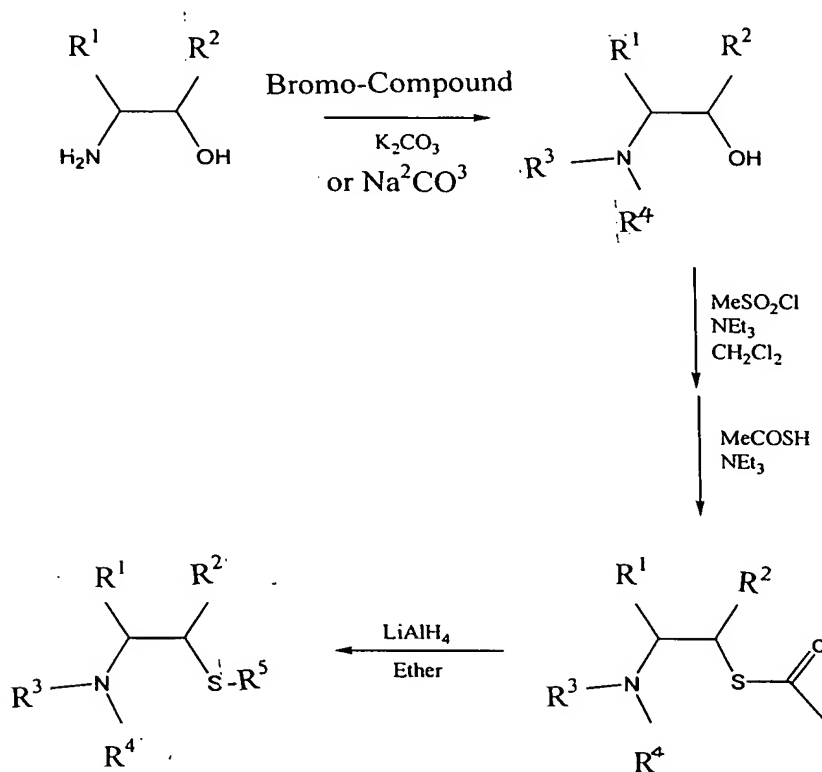
R^4 is aryl or alkyl of C1-C9; or

5 R^3 , R^4 and N can form a three-to-eight-membered heterocycle; and

R^5 can be H or alkyl of C1-C6.

【Preparation Mode】

10 In general, the aminothiols can be prepared through procedures shown in Scheme A.



Scheme A

15

Scheme A includes steps of: (a) reacting amino-alcohol with bromo-compound and carbonate of alkaline metal to form the specific ligand of R^3 , R^4 and N; (b) replacing $-OH$ with $-SAc$ by adding $MeSO_2Cl$ and NEt_3 (c) adding $LiAlH_4$ to form $-SH$.

20

The following EXAMPLEs indicate procedures for preparing

representative aminothiols of the present invention. Table 1 lists codes of different ligands shown in the compound of formula (I), so that the aminothiols of the present invention can be simply represented with combinations of such codes.

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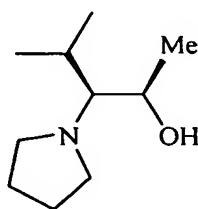
Table 1

R ¹		R ²		N-R ³ -R ⁴		R ⁵	
code	ligand	code	ligand	code	ligand	code	ligand
2	methyl	b	methyl	2	Bu ⁿ (n-butyl)	c	H
3	Bu ⁿ (n-butyl)	c	Bu ⁿ (n-butyl)	3	Bn (benzyl)		
4	i-butyl	f	i-propyl	4	pyrrolidinyl		
5	Bn (benzyl)	g	Ph (phenyl)	5	piperidyl		
6	i-propyl			6	morpholinyl		
7	Ph (phenyl)						

For example, compound (2b4c) is an aminothiol compound of the present invention, wherein R¹ is methyl; R² is methyl; N, R³ and R⁴ form a five-membered heterocycle, pyrrolidinyl; and R⁵ is H. As for the middle product obtained in step (a), the last code "a" represents the alcohol ligand, -OH.

EXAMPLES 1 and 2: Preparation of (2*R*,3*S*)-4-Methyl-3-(1-pyrrolidinyl) pentane-2-thiol (6b4c) and
(3*R*,4*S*)-2-Methyl-4-(1-pyrrolidinyl) pentane-3-thiol (2f4c)
Step (a): Preparing (2*R*,3*S*)-4-Methyl-3-(1-pyrrolidinyl) pentan-2-ol (6b4a)

20



To a three-necked flask, (2*R*,3*S*)-3-amino-4-methylpentan-2-ol (0.585g, 5.0 mmol), Na₂CO₃ (1.16g, 11.0 mmol) and CH₃CN (20mL) are added under the nitrogen system and then heated with refluxing. Next,
5 Br₂C₄H₈ (1.295g, 6.0 mmol) is injected into the solution. After complete reaction for 12 hours, H₂O (20mL) is added to terminate the reaction. The product is repeatedly extracted with EtOAc (20mL), wherein the organic phase is dehydrated with Na₂SO₄. A coarse product is obtained after filtration and concentration. Column chromatography (Silica gel 50g, eluent is
10 n-Hexane:EtOAc = 1:1) is used to purify the coarse product and a slightly-yellow liquid (0.85g) is obtained. The yield is 85% and the other analysis includes:

¹H NMR (400 MHz, CDCl₃)

15 δ 0.87 (d, J=6.4 Hz, 3H, CH(CH₃)₂), 0.96 (d, J=6.4 Hz, 3H, CH(CH₃)₂), 1.05 (d, J=6.4 Hz, 3H, CHOHCH₃), 1.72-1.79 (m, 4H, -(CH₂)₂-), 1.82-2.00 (m, 1H, CH(CH₃)₂), 2.48 (dd, J₁=4.8 Hz, J₂=10.0 Hz, 1H, NCH), 2.80-2.92 (m, 4H, NCH₂-), 3.70-3.80 (m, 1H, CHOH)

¹³C NMR (100 MHz, CDCl₃)

20 δ 18.59 (CHOHCH₃), 19.80 (CH(CH₃)₂), 21.38 (CH(CH₃)₂), 23.93 (-CH₂-) 27.30 (CH(CH₃)₂), 50.91 (NCH₂-), 65.64 (NCH), 69.50 (CHOH)

Element analysis: C₁₀H₂₁NO

theoretical: C, 70.12; H, 12.36; N, 8.18

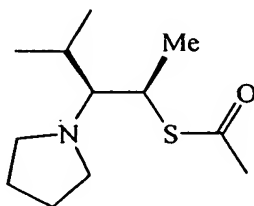
25 experimental: C, 71.16; H, 12.28; N, 8.14

High-resolution MS (70eV) m/e theoretical: 171.1623

experimental: 172.1699

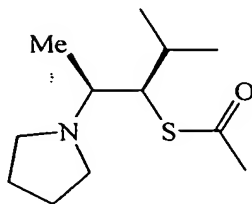
[α]_D²⁵ = + 42.1 (c=1.45, CDCl₃)

30 Step (b): Preparing (2*R*,3*S*)-4-Methyl-3-(1-pyrrolidinyl)-2-thioacetylpentane (6b4b)



5 and (3*R*,4*S*)-2-Methyl-4-(1-pyrrolidinyl)-3-thioacetylpentane (**2f4b**)

10



15 To a three-necked flask, compound (**6b4a**) (0.855g, 5.0 mmol),
CH₂Cl₂ (20mL) and NEt₃ (1.01g, 10.0 mmol) are added under nitrogen
system. Next, MeSO₂Cl (0.69g, 6.0 mmol, dissolved in 20mL CH₂Cl₂) is
added dropwisely at 0°C. After complete reaction for 2 hours, a coarse
product is obtained through repeated depressing concentration and adding
benzene therein. The coarse product is then added into benzene (20mL) with
20 refluxing, and MeCOSH (0.46g, 6.0 mmol) and NEt₃ (1.01g, 10.0 mmol)
dissolved in 20mL benzene are injected into the above solution under the
nitrogen system. After 12 hours, H₂O (20mL) is added to terminate the
reaction. The product is repeatedly extracted with EtOAc (20mL), wherein
the organic phase is dehydrated with Na₂SO₄. A coarse product is obtained
25 after filtration and concentration. Column chromatography (Silica gel 70g,
eluent is n-Hexane:NEt₃ = 100:1) is used to purify the coarse product and
two orange liquids, compound (**6b4b**) (0.229g) and compound (**2f4b**)
(0.458g), are obtained. The yields of compound (**6b4b**) and compound (**2f4b**)
are 20% and 40%, respectively. The other analysis for compound (**6b4b**)
30 includes:

¹H NMR (400 MHz, CDCl₃)

δ 0.92 (d, J=7.2 Hz, 3H, CH(CH₃)₂), 0.94 (d, J=7.2 Hz, 3H,
CH(CH₃)₂), 1.27 (d, J=6.8 Hz, 3H, SCHCH₃), 1.66-1.73 (m, 4H,
-(CH₂)₂-), 1.90-2.05 (m, 1H, CH(CH₃)₂), 2.27 (s, 3H, SCOCH₃),

2.41 (dd, $J_1=3.2$ Hz, $J_2=8.0$ Hz, 1H, NCH), 2.67-2.74 (m, 2H, NCH₂-), 2.75-2.81 (m, 2H, NCH₂-), 3.86-4.05 (m, 1H, SCH)

¹³C NMR (100 MHz, CDCl₃)

5 δ 18.38 (SCHCH₃) 20.37 (CH(CH₃)₂), 21.18 (CH(CH₃)₂), 24.20 (-CH₂-), 29.40 (CH(CH₃)₂), 30.66 (SCOCH₃), 43.29 (NCH) 51.06 (NCH₂-), 69.61 (SCHCH₃), 196.77 (SCOCH₃)

Element analysis C₁₂H₂₃NOS

theoretical: C, 62.83; H, 10.11; N, 6.11

experimental: C, 62.90; H, 10.10; N, 6.02

10 High-resolution MS (70eV) m/e theoretical: 229.1500

experimental: 229.1523

[α]_{25D} = +48.1° (c=1.05, CDCl₃)

The other analysis for compound (2f4b) includes:

15 ¹H NMR (400 MHz, CDCl₃)

δ 0.91 (d, $J=6.8$ Hz, 3H, CH(CH₃)₂), 0.96 (d, $J=7.2$ Hz, 3H, CH(CH₃)₂), 1.03 (d, $J=6.8$ Hz, 3H, NCHCH₃), 1.68-1.73 (m, 4H, -(CH₂)₂-), 1.86-2.11 (m, 1H, CH(CH₃)₂), 2.33 (s, 3H, SCOCH₃), 2.42-2.64 (m, 4H, NCH₂-), 2.42-2.64 (m, 1H, NCH), 3.60 (dd, $J_1=4.8$ Hz, $J_2=8.0$ Hz, 1H, SCH),

20

¹³C NMR (100 MHz, CDCl₃)

δ 13.78 (NCHCH₃) 19.81 (CH(CH₃)₂), 20.78 (CH(CH₃)₂), 23.26 (-CH₂-), 30.25 (CH(CH₃)₂), 30.72 (SCOCH₃), 50.64 (NCH₂-), 54.84 (NCH), 58.89 (SCHCH₃), 195.56 (SCOCH₃)

25 Element analysis C₁₂H₂₃NOS

theoretical: C, 62.83; H, 10.11; N, 6.11

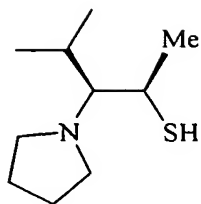
experimental: C, 62.56; H, 10.25; N, 5.97

High-resolution MS (70eV) m/e theoretical: 299.1500

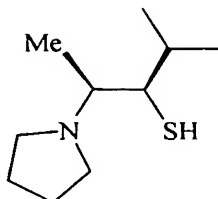
experimental: 299.1508

30 [α]_{25D} = +41.7° (c = 0.99, CDCl₃)

Step (c): Preparing (2*R*,3*S*)-4-Methyl-3- (1-pyrrolidinyl)pentane-2-thiol (6b4c)



and (3*R*,4*S*)-2-Methyl-4-(1-pyrrolidinyl)pentane-3-thiol (**2f4c**)



To a three-necked flask, LAH (LiAlH_4 , 0.076g, 2.0 mmol) and ether (10mL) are added under nitrogen system. Next, compound (**6b4b**) (0.229g, 1.0mmol) or compound (**2f4b**) (0.229g, 1.0 mmol) dissolved in 10mL ether is slowly added into the flask within 30min at 0°C . After reaction for 1 hour, 15% NaOH is added to the flask until a white solid is present complete. The solid is filtered and repeatedly washed with a solvent. The filtrate is then concentrated to obtain a coarse product. Column chromatography (Silica gel 40g, eluent is n-Hexane: NEt_3 = 100:1) is used to purify the coarse product and two orange liquids, compound (**6b4c**) (0.15g) and compound (**2f4c**) (0.15g), are obtained. The yields of compound (**6b4c**) and compound (**2f4b**) are 80% and 80%, respectively. The other analysis for compound (**6b4c**) includes:

^1H NMR (400 MHz, CDCl_3)

δ 0.88 (d, $J=6.8$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 0.93 (d, $J=6.4$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 1.35 (d, $J=6.8$ Hz, 3H, CHSHCH_3), 1.65-1.73 (m, 4H, $-(\text{CH}_2)_2-$), 1.98-2.10 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.55 (dd, $J_1=3.6$ Hz, $J_2=7.2$ Hz, 1H, NCH), 2.70-2.75 (m, 2H, NCH_2-), 2.76-2.82 (m, 2H, NCH_2-), 3.03-3.20 (m, 1H, CHOH)

^{13}C NMR (100 MHz, CDCl_3)

δ 20.75 (CH(CH₃)₂), 21.24 (CHSHCH₃), 22.26 (CH(CH₃)₂), 24.49 (-CH₂-) 29.17 (CH(CH₃)₂), 38.44 (NCH), 51.18 (NCH₂-), 70.87 (SCH)

Element analysis C₁₀H₂₁NS

5 theoretical: C, 64.11; H, 11.30; N, 7.48
experimental: C, 64.35; H, 11.12; N, 7.65

High-resolution MS (70eV) m/e theoretical: 187.1395
experimental: 187.1366

[α]_{25D} = +17.4° (c=0.83, CDCl₃)

10

The other analysis for compound (2f4c) includes:

¹H NMR (400 MHz, CDCl₃)

15 δ 0.92 (d, J=6.8 Hz, 3H, CH(CH₃)₂), 1.01 (d, J=6.4 Hz, 3H, CH(CH₃)₂), 1.04 (d, J=6.4 Hz, 3H, NCHCH₃), 1.69-1.75 (m, 4H, -(CH₂)₂-), 1.69-1.75 (m, 1H, CH(CH₃)₂), 2.35-2.41 (m, 1H, NCH), 2.43-2.49 (m, 2H, NCH₂-), 2.52-2.58 (m, 2H, NCH₂-), 2.84 (dd, J₁=4.0 Hz, J₂=9.6 Hz, 1H, SHCH)

¹³C NMR (100 MHz, CDCl₃)

20 δ 12.08 (NCHCH₃), 20.47 (CH(CH₃)₂), 21.71 (CH(CH₃)₂), 23.27 (-CH₂-) 31.24 (CH(CH₃)₂), 50.95 (NCH₂-), 52.17 (NCH), 60.54 (SCH)

Element analysis C₁₀H₂₁NS

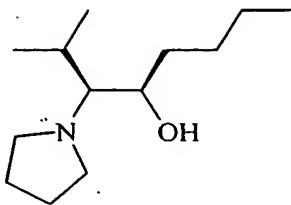
theoretical: C, 64.11; H, 11.30; N, 7.48
experimental: C, 63.98; H, 11.25; N, 7.45

25 High-resolution MS (70eV) m/e theoretical: 187.1395
experimental: 187.1386

[α]_{25D} = +23.7° (c = 1.51, CDCl₃)

30 EXAMPLEs 3 and 4: Preparation of (3*S*,4*R*)-2-Methyl-3-(1-pyrrolidinyl) octane-4-thiol (6c4c) and (3*R*,4*S*)-2-Methyl-4-(1-pyrrolidinyl) octane-3-thiol (3f4c)

Step (a): Preparing (3*S*,4*R*)-2-Methyl-3-(1-pyrrolidinyl)octan-4-ol (6c4a)



5

Repeat Step (a) of EXAMPLE 1, but (2*R*,3*S*)-3-amino-4-methylpentan-2-ol is replaced with (3*S*,4*R*)-3-amino-2-methyloctan-4-ol. The analysis for compound

(**6c4a**) includes:

10 ¹H NMR (400 MHz, CDCl₃)

δ 0.77-0.92 (m, 3H, (CH₂)₃CH₃), 0.77-0.92 (m, 6H, CH(CH₃)₂), 1.06-1.62 (m, 6H, (CH₂)₃CH₃), 1.62-1.81 (m, 4H, -(CH₂)₂-), 1.89-2.05 (m, 1H, CH(CH₃)₂), 2.47 (dd, J₁=4.8 Hz, J₂=9.6 Hz, 1H, NCH), 2.74-2.86 (m, 4H, NCH₂-), 3.45-3.52 (m, 1H, CHOH),

15 ¹³C NMR (100 MHz, CDCl₃)

δ 13.99 (CH₂CH₂CH₂CH₃), 20.20 (CH(CH₃)₂), 21.81 (CH(CH₃)₂), 22.66 (CH₂CH₂CH₂CH₃), 24.23 (-CH₂-), 27.48 (CH(CH₃)₂), 29.23 (CH₂CH₂CH₂CH₃), 32.21 (CH₂CH₂CH₂CH₃), 50.85 (NCH₂-), 69.11 (NCH), 70.58 (CHOH)

20 Element analysis C₁₃H₂₇NO

theoretical: C, 73.18; H, 12.76; N, 6.56

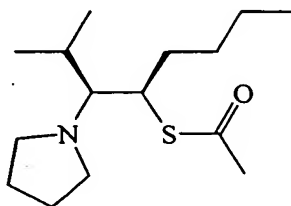
experimental: C, 73.20; H, 12.63; N, 6.51

High-resolution MS (70eV) m/e theoretical: 213.2093

experimental: 214.2165

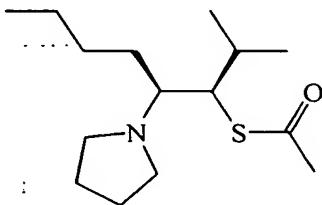
25 [α]_D²⁵ = +53.3° (c=1.03, CDCl₃)

Step (b): Preparing (3*S*,4*R*)-2-Methyl-3-(1-pyrrolidinyl)-4-thioacetyloctane (**6c4b**)



30

and (3*R*,4*S*)-2-Methyl-4-(1-pyrrolidinyl)-3-thioacetyloctane (**3f4b**)



Repeat Step (b) of EXAMPLE 1, but replace compound (**6b4a**) with compounds (**6c4a**) or (**3f4a**). Analysis for product (**6c4b**) includes:

10 ^1H NMR (400 MHz, CDCl_3)

δ 0.85 (t, $J=7.2$ Hz, 3H, $(\text{CH}_2)_3\text{CH}_3$), 0.86 (d, $J=5.6$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 0.95 (d, $J=5.6$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 1.20-1.50 (m, 6H, $(\text{CH}_2)_3\text{CH}_3$), 1.64-1.72 (m, 4H, $-(\text{CH}_2)_2-$), 1.85-2.12 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.28 (s, 3H, SCOCH_3), 2.43 (dd, $J_1=2.8$ Hz, $J_2=8.0$ Hz, 1H, NCH), 2.58-2.66 (m, 2H, NCH_2-), 2.68-2.77 (m, 2H, NCH_2-), 3.80-3.88 (m, 1H, SCH),

^{13}C NMR (100 MHz, CDCl_3)

δ 14.00 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 20.50 ($\text{CH}(\text{CH}_3)_2$), 21.19 ($\text{CH}(\text{CH}_3)_2$), 22.56 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 23.99 ($-\text{CH}_2-$), 29.54 ($\text{CH}(\text{CH}_3)_2$), 29.58 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 30.53 (SCOCH_3), 32.16 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 47.53 (NCH), 50.79 (NCH_2-), 70.19 (SCH), 196.26 (SCOCH_3)

Element analysis $\text{C}_{15}\text{H}_{29}\text{NOS}$

theoretical: C, 66.37; H, 10.77; N, 5.16

experimental: C, 66.14; H, 10.85; N, 5.22

25 High-resolution MS (70eV) m/e theoretical: 271.1970

experimental: 271.1971

$[\alpha]_{25\text{D}} = +39.6^\circ$ ($c=1.03$, CDCl_3)

Analysis for product (**3f4b**) includes:

30 ^1H NMR (400 MHz, CDCl_3)

δ 0.82-0.90 (m, 3H, $(\text{CH}_2)_3\text{CH}_3$), 0.82-0.90 (m, 3H, $\text{CH}(\text{CH}_3)_2$), 0.93 (d, $J=6.4$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 1.20-1.60 (m, 6H, $(\text{CH}_2)_3\text{CH}_3$), 1.65-1.73 (m, 4H, $-(\text{CH}_2)_2-$), 1.91-2.05 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.31 (s, 3H, SCOCH_3), 2.50-2.63 (m, 4H, NCH_2-), 2.50-2.63 (m, 1H,

NCH), 3.63 (t, J=6.0 Hz, 1H, SCH),

¹³C NMR (100 MHz, CDCl₃)

δ 13.91 (CH₂CH₂CH₂CH₃), 19.07 (CH(CH₃)₂), 20.83 (CH(CH₃)₂),
22.98 (CH₂CH₂CH₂CH₃), 23.56 (-CH₂-), 30.26 (CH(CH₃)₂), 30.49
(CH₂CH₂CH₂CH₃), 30.70 (SCOCH₃), 30.79 (CH₂CH₂CH₂CH₃),
49.33 (NCH₂-), 53.70 (NCH), 61.89 (SCH), 195.68 (SCOCH₃)

Element analysis C₁₅H₂₉NOS

theoretical: C, 66.37; H, 10.77; N, 5.16

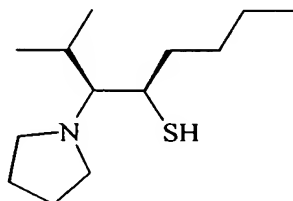
experimental: C, 66.23; H, 10.71; N, 5.02

High-resolution MS (70eV) m/e theoretical: 271.1970

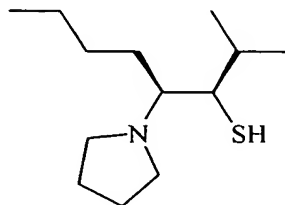
experimental: 271.1991

[α]_D²⁵ = +48.2° (c = 1.24, CDCl₃)

Step (c): Preparing (3*S*,4*R*)-2-Methyl-3-(1-pyrrolidinyl)octane-4-thiol (**6c4c**)



and (3*R*,4*S*)-2-Methyl-4-(1-pyrrolidinyl) octane-3-thiol (**3f4c**)



Repeat Step (c) of EXAMPLE 1, but replace compound (**6b4b**) with compounds (**6c4b**) or (**3f4b**). Analysis for product (**6c4c**) includes:

¹H NMR (400 MHz, CDCl₃)

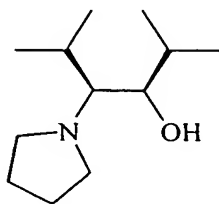
δ 0.84-1.00 (m, 6H, CH(CH₃)₂), 0.84-1.00 (m, 3H, (CH₂)₃CH₃),
1.16-1.35 (m, 4H, CH₂(CH₂)₂CH₃), 1.48-1.78 (m, 2H,
CH₂(CH₂)₂CH₃), 1.48-1.78 (m, 4H, -(CH₂)₂-), 2.00-2.13 (m, 1H,
CH(CH₃)₂), 2.43 (dd, J₁=3.6 Hz, J₂=8.4 Hz, 1H, NCH), 2.71-2.93

- (m, 4H, NCH₂-), 2.71-2.963 (m, 1H, SHCH),
¹³C NMR (100 MHz, CDCl₃)
 δ 14.07 (CH₂CH₂CH₂CH₃), 20.88 (CH(CH₃)₂), 21.39 (CH(CH₃)₂),
 22.49 (CH₂CH₂CH₂CH₃), 24.39 (-CH₂-), 28.90 (CH(CH₃)₂), 30.54
 5 (CH₂CH₂CH₂CH₃), 34.56 (CH₂CH₂CH₂CH₃), 44.95 (NCH), 51.01
 (NCH₂-), 70.85 (CHSH)
 Element analysis C₁₃H₂₇NS
 theoretical: C, 68.06; H, 11.86; N, 6.11
 experimental: C, 68.21; H, 11.55; N, 6.35
 10 High-resolution MS (70eV) m/e theoretical: 229.1864
 experimental: 229.1857
 [α]_{25D} = +54.3° (c=1.01, CDCl₃)
- Analysis for product (3f4c) includes:
 15 ¹H NMR (400 MHz, CDCl₃)
 δ 0.86-1.00 (m, 3H, (CH₂)₃CH₃), 0.86-1.00 (m, 6H, CH(CH₃)₂),
 1.23-1.50 (m, 4H, CH₂(CH₂)₂CH₃), 1.52-1.73 (m, 2H,
 CH₂(CH₂)₂CH₃), 1.52-1.73 (m, 4H, -(CH₂)₂-), 1.75-1.92 (m, 1H,
 CH(CH₃)₂), 2.33 (dd, J₁=4.4 Hz, J₂=8.0 Hz, 1H, NCH), 2.47-2.62
 20 (m, 4H, NCH₂-), 2.85 (dd, J₁=4.4 Hz, J₂=8.0 Hz, 1H, SHCH),
¹³C NMR (100 MHz, CDCl₃)
 δ 13.92 (CH₂CH₂CH₂CH₃), 20.13 (CH(CH₃)₂), 21.23 (CH(CH₃)₂),
 23.21 (CH₂CH₂CH₂CH₃), 23.43 (-CH₂-), 29.30 (CH₂CH₂CH₂CH₃),
 30.65 (CH(CH₃)₂), 31.42 (CH₂CH₂CH₂CH₃), 50.24 (NCH₂-), 51.99
 25 (NCH), 64.56 (CHSH)
 Element analysis C₁₃H₂₇NS
 theoretical: C, 68.06; H, 11.86; N, 6.11
 experimental: C, 68.21; H, 11.56; N, 6.01
 High-resolution MS (70eV) m/e theoretical: 229.1864
 30 experimental: 229.1857
 [α]_{25D} = +38.8° (c = 0.99, CDCl₃)

EXAMPLE 5: Preparation of

(3*R*,4*S*)-2,5-Dimethyl-4-(1-pyrrolidiny)hexane- 3-thiol (6f4c)

Step (a): Preparing (3*R*,4*S*)-2,5-Dimethyl-4-(1-pyrrolidinyl)hexan-3-ol (6f4a)



Repeat Step (a) of EXAMPLE 1, but replace (2*R*,3*S*)-3-amino-4-methylpentan-2-ol with (3*R*,4*S*)-4-amino-2,5-dimethylhexan-3-ol. Analysis for compound (6f4a) includes:

¹H NMR (400 MHz, CDCl₃)

δ 0.83 (d, J=6.8 Hz, 3H, NCHCH(CH₃)₂), 0.97 (d, J=6.8 Hz, 3H, NCHCH(CH₃)₂), 1.02 (d, J=1.2 Hz, 3H, CHOHCH(CH₃)₂), 1.04 (d, J=1.2 Hz, 3H, CHOHCH(CH₃)₂), 1.63-1.73 (m, 4H, -(CH₂)₂-), 1.74-1.83 (m, 1H, NCHCH(CH₃)₂), 2.05-2.12 (m, 1H, CHOHCH(CH₃)₂), 2.21 (dd, J₁=3.2 Hz, J₂=4.0 Hz, 1H, NCH), 2.55-2.63 (m, 2H, NCH₂-), 2.65-2.72 (m, 2H, NCH₂-), 3.41 (dd, J₁=4.4 Hz, J₂=9.2 Hz, 1H, CHOH)

¹³C NMR (100 MHz, CDCl₃)

δ 19.20 (NCHCH(CH₃)₂), 19.30 (NCHCH(CH₃)₂), 19.62 (CHOHCH(CH₃)₂), 22.68 (CHOHCH(CH₃)₂), 23.40 (-CH₂-), 26.99 (NCHCH(CH₃)₂), 30.59 (CHOHCH(CH₃)₂), 51.59 (NCH₂-), 68.34 (NCH), 77.60 (CHOH)

Element analysis C₁₂H₂₅NO

theoretical: C, 72.31; H, 12.64; N, 7.03

experimental: C, 72.18; H, 12.73; N, 6.89

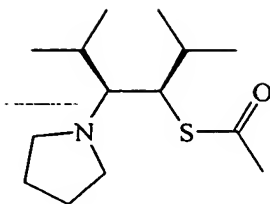
High-resolution MS (70eV) m/e theoretical: 199.1936

experimental: 200.2011

[α]_D²⁵ = +45.7° (c=1.21, CDCl₃)

Step (b): Preparing

(3*R*,4*S*)-2,5-Dimethyl-4-(1-pyrrolidinyl)-3-thioacetylhexane (6f4b)



5

Repeat Step (b) of EXAMPLE 1, but replace compound (6b4a) with compound (6f4a). Analysis for product (6f4b) includes:

¹H NMR (400 MHz, CDCl₃)

10 δ 0.88 (d, J=6.8Hz, 3H, NCHCH(CH₃)₂), 0.90-0.98 (m, 3H, NCHCH(CH₃)₂), 0.90-0.98 (m, 6H, SCHCH(CH₃)₂), 1.66-1.71 (m, 4H, -(CH₂)₂-), 1.88-2.00 (m, 1H, NCHCH(CH₃)₂), 2.01-2.12 (m, 1H, SCHCH(CH₃)₂), 2.34 (s, 3H, SCOCH₃), 2.62-2.70 (m, 2H, NCH₂-), 2.71-2.77 (m, 2H, NCH₂-), 2.62-2.77 (m, 1H, NCH), 3.79 (dd,

15 J₁=5.2Hz, J₂=6.4Hz, 1H, SCH)

¹³C NMR (100 MHz, CDCl₃)

δ 18.62 (NCHCH(CH₃)₂), 19.99 (NCHCH(CH₃)₂), 21.10 (SCHCH(CH₃)₂), 21.59 (SCHCH(CH₃)₂), 24.01 (-CH₂-), 30.44 (NCHCH(CH₃)₂), 30.54 (SCHCH(CH₃)₂), 30.70 (SCOCH₃), 49.24 (NCH₂-), 50.80 (NCH), 64.73 (SCH), 195.37 (SCOCH₃)

20

Element analysis C₁₄H₂₇NOS

theoretical: C, 65.32; H, 10.57; N, 5.44

experimental: C, 65.20; H, 10.81; N, 5.14

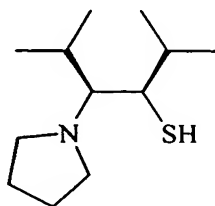
High-resolution MS (70eV) m/e theoretical: 257.1813

25 experimental: 257.1859

[α]_D²⁵ = +53.9° (c=1.23, CDCl₃)

Step (c): Preparing (3R,4S)-2,5-Dimethyl-4-(1-pyrrolidinyl)hexane-3-thiol (6f4c)

30



methylpentan-2-ol with (1*R*,2*S*)-2-amino-3-methyl-1-phenylbutan-1-ol, and replace Na₂CO₃ (1.16g, 11.0 mmol) with K₂CO₃ (1.52g, 11.0 mmol). Column chromatography (Silica gel, eluent is n-Hexane:EtOAc = 10:1) is used to purify the coarse product and a slightly-yellow liquid (1.00g) is obtained. The yield is 86% and the other analysis includes:

¹H NMR (400 MHz, CDCl₃)

δ 0.80 (d, J=6.8 Hz, 3H, CH(CH₃)₂), 0.96 (d, J=6.8 Hz, 3H, CH(CH₃)₂), 1.62-1.70 (m, 4H, -(CH₂)₂-), 1.72-1.82 (m, 1H, CH(CH₃)₂), 2.54 (dd, J₁=4.4 Hz, J₂=8.0 Hz, 1H, NCH), 2.57-2.64 (m, 2H, NCH₂-), 2.68-2.74 (m, 2H, NCH₂-), 4.92 (d, J=4.0 Hz, 1H, CHOH), 7.14-7.34 (m, 5H, ArH)

¹³C NMR (100 MHz, CDCl₃)

δ 20.28 (CH(CH₃)₂), 21.81 (CH(CH₃)₂), 23.78 (-CH₂-), 27.88 (CH(CH₃)₂), 51.47 (NCH₂-), 72.29 (NCH), 72.51 (CHOH), 126.08, 126.62, 127.79, 142.88 (Ph)

Element analysis C₁₅H₂₃NO

theoretical: C, 77.21; H, 9.93; N, 6.00

experimental: C, 77.11; H, 9.73; N, 6.23

High-resolution MS (70eV) m/e theoretical: 233.1780

experimental: 234.1865

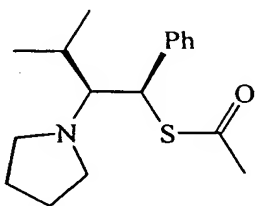
[α]_D²⁵ = -41.3° (c=1.38, CDCl₃)

Step

(b):

Preparing

(1*R*,2*S*)-3-Methyl-1-phenyl-2-(1-pyrrolidinyl)-1-thioacetyl butane
(**6g4b**)



Repeat Step (b) of EXAMPLE 1, but replace compound (**6b4a**) with compound (**6g4a**). Column chromatography (Silica gel, eluent is n-Hexane:NEt₃ = 100:1) is used to purify the coarse product and a

slightly-yellow liquid (1.09g) is obtained. The yield is 75% and the other analysis includes:

^1H NMR (400MHz, CDCl_3)

5 δ 0.90 (d, $J=6.8$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 0.99 (d, $J=6.4$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 1.45-1.55 (m, 4H, $-(\text{CH}_2)_2-$), 1.92-2.04 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.26 (s, 3H, SCOCH_3), 2.60-2.69 (m, 4H, NCH_2-), 2.97 (t, $J=6.4$ Hz, 1H, NCH), 4.99 (d, $J=6.4$ Hz, 1H, SCH), 7.14-7.41 (m, 5H, ArH)

^{13}C NMR (100 MHz, CDCl_3)

10 δ 19.82 ($\text{CH}(\text{CH}_3)_2$), 21.62 ($\text{CH}(\text{CH}_3)_2$), 24.31 ($-\text{CH}_2-$), 30.57 ($\text{CH}(\text{CH}_3)_2$), 30.59 (SCOCH_3), 49.69 (NCH), 50.42 (NCH_2-), 69.33 (SCH), 126.73, 127.86, 128.70, 141.80 (Ph), 194.60 (SCOCH_3)

Element analysis $\text{C}_{17}\text{H}_{25}\text{NOS}$

theoretical: C, 70.06; H, 8.65; N, 4.81

15 experimental: C, 69.68; H, 8.80; N, 4.63

High-resolution MS (70eV) m/e theoretical: 291.1657

experimental: 291.1661

$[\alpha]_{25\text{D}} = -240.8^\circ$ ($c=1.02$, CDCl_3)

20

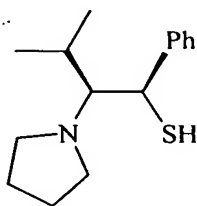
Step

(c):

Preparing

(1*R*,2*S*)-3-Methyl-1-phenyl-2-(1-pyrrolidinyl)butane-1-thiol (**6g4c**)

25



30 Repeat Step (c) of EXAMPLE 1, but replace compound (**6b4b**) with compound (**6g4b**). A slightly-yellow liquid (0.401g) is obtained through pumping concentration. The yield is 85% and other analysis includes:

^1H NMR (400 MHz, CDCl_3)

δ 0.95 (d, $J=7.2$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 0.99 (d, $J=6.4$ Hz, 3H, $\text{CH}(\text{CH}_3)_2$), 1.37-1.48 (m, 4H, $-(\text{CH}_2)_2-$), 2.06-2.15 (m, 1H,

^{13}C NMR (100 MHz, CDCl_3)Element analysis $\text{C}_{15}\text{H}_{23}\text{NS}$

10 experimental: C, 72.01; H, 9.88; N, 5.32

experimental: 249.1554

EXAMPLE 7: Preparation of (1R,2S)-1,2-Diphenyl-2-piperidin-1-yl-ethanethiol (**6g5c**)

CC(C)[C@H](N1CCCC1)[C@H](O)C2=CC=CC=C2¹H NMR (400MHz , CDCl₃) ^{13}C NMR (100MHz , CDCl_3)

19

($\underline{\text{C}}\text{H}(\text{CH}_3)_2$), 51.47 (NCH_2-), 72.29 (NCH), 72.51 ($\underline{\text{C}}\text{HOH}$),
126.08, 126.62, 127.79, 142.88 (Ph)

Element analysis $\text{C}_{18}\text{H}_{21}\text{NO}$

theoretical: C, 77.21 ; H, 9.93 ; N, 6.00

5 experimental: C, 77.11 ; H, 9.73 ; N, 6.91

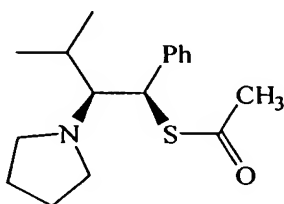
High-resolution MS (70eV) m/e theoretical: 233.1780

experimental: 234.1865

$[\alpha]_D^{25} = -41.3$ ($c = 1.38$, CHCl_3)

10 Step (b): Preparing (1R,2S)-Thioavcetic
acidS-(3-methyl-1-phenyl-2-pyrrolidin-1-yl-butyl)ester (6g5b)

15



20

Repeat Step (b) of EXAMPLE 6, but replace compound (6g4a) with compound (6g5a). Column chromatography (Silica gel, eluent is n-Hexane:NEt₃ = 100:1) is used to purify the coarse product and a slightly-yellow liquid (1.09g) is obtained. The yield is 75% and the other analysis includes:

^1H NMR (400MHz , CDCl_3)

25

δ 0.90 (d, $J=6.8\text{Hz}$, 3H, $\text{CH}(\underline{\text{C}}\text{H}_3)_2$), 0.99 (d, $J=6.4\text{Hz}$, 3H, $\text{CH}(\underline{\text{C}}\text{H}_3)_2$), 1.45-1.55 (m, 4H, $-(\underline{\text{C}}\text{H}_2)_2-$), 1.92-2.04 (m, 1H, $\underline{\text{C}}\text{H}(\text{CH}_3)_2$), 2.26 (s, 3H, SCOCH_3), 2.60-2.69 (m, 4H, NCH_2-), 2.97 (t, $J=6.4\text{Hz}$, 1H, NCH), 4.99 (d, $J=6.4\text{Hz}$, 1H, SCH), 7.14-7.41 (m, 5H, ArH)

^{13}C NMR (100MHz , CDCl_3)

30

δ 19.82 ($\text{CH}(\underline{\text{C}}\text{H}_3)_2$), 21.62 ($\text{CH}(\underline{\text{C}}\text{H}_3)_2$), 24.31 ($-\text{CH}_2-$), 30.57 ($\underline{\text{C}}\text{H}(\text{CH}_3)_2$), 30.59 (SCOCH_3), 49.69 (NCH), 50.42 (NCH_2-), 69.33 ($\underline{\text{C}}\text{HSCOCH}_3$), 126.73, 127.86, 128.70, 141.80 (Ph), 194.60 (SCOCH_3)

Element analysis $\text{C}_{21}\text{H}_{25}\text{NOS}$

theoretical: C, 70.06; H, 8.65; N, 4.81; S 11.00

experimental: C, 69.68; H, 8.80; N, 4.63; S 11.13

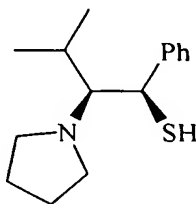
High-resolution MS (70eV) m/e theoretical: 291.1657

experimental: 291.1661

5 $[\alpha]_D^{25} = -240.8$ (c = 1, CHCl₃)

Step (c): Preparing (1R,2S)-
3-Methyl-1-phenyl-2-pyrrolidin-1-yl-butane-1-thiol (**6g5c**)

10



15 Repeat Step (c) of EXAMPLE 6, but replace compound (**6g4b**) with compound (**6g5b**). A slightly-yellow liquid (0.401g) is obtained. The yield is 85%, and the other analysis includes:

¹H NMR (400MHz , CDCl₃)

20 δ 0.95 (d, J=7.2Hz, 3H, CH(CH₃)₂), 0.99 (d, J=6.4Hz, 3H, CH(CH₃)₂), 1.37-1.48 (m, 4H, -(CH₂)₂-), 2.06-2.15 (m, 1H, CH(CH₃)₂), 2.54-2.70 (m, 4H, NCH₂-), 3.00 (dd, J₁=5.2Hz, J₂=7.6Hz, 1H, NCH), 4.30 (d, J=7.6Hz, 1H, SHCH), 7.12-7.40 (m, 5H, ArH)

¹³C NMR (100MHz , CDCl₃)

25 δ 18.95 (CH(CH₃)₂), 21.67 (CH(CH₃)₂), 24.46 (-CH₂-), 30.42 (CH(CH₃)₂), 50.60 (NCH₂-), 70.03 (NCH), 77.20 (CHSH), 126.73, 127.9, 128.1, 144.57 (Ph),

Element analysis C₂₄H₃₃NOS

theoretical: C, 72.23; H, 9.29; N, 5.62

30 experimental: C, 72.01; H, 9.88; N, 5.32

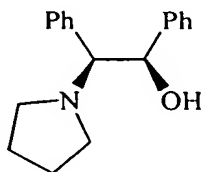
High-resolution MS (70eV) m/e theoretical: 249.1551

experimental: 249.1554

$[\alpha]_D^{25} = -489.0$ (c = 1, CHCl₃)

EXAMPLE 8: Preparation of
 (1R,2S)-1,2-Diphenyl-2-piperidin-1-yl-ethanethiol (**7g4c**)
 Step (a): Preparing (1R,2S)-1,2-Diphenyl-2-pyrrolidine-1-yl-ethanol (**6g5a**)

5



Repeat Step (a) of EXAMPLE 6, but replace
 10 (1R,2S)-2-amino-1-phenyl-3-methyl-butanol with
 (1R,2S)-2-amino-1,2-diphenyl-ethanol. Column chromatography (Silica gel,
 eluent is n-Hexane:EtOAc = 5:1) is used to purify the coarse product and a
 white solid (1.24g) is obtained. The yield is 93% and the other analysis
 includes:

15 ^1H NMR (400MHz , CDCl_3)
 δ 1.82-1.85 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.59-2.62 (m, 2H, NCH_2),
 2.74-2.76 (m, 2H, NCH_2), 3.30 (d, $J = 3.2\text{Hz}$, 1H, NCH), 5.24 (d,
 $J = 3.0\text{Hz}$, 1H, CHOH), 6.97-7.25 (m, 10H, ArH)

^{13}C NMR (100MHz , CDCl_3)
 20 δ 23.47 ($\text{N}(\text{CH}_2\text{CH}_2)_2$), 52.94 ($\text{N}(\text{CH}_2)_2$), 73.99 (NCH), 77.31
 (CHOH), 126.08, 126.70, 127.02, 127.19, 127.42, 129.25, 137.47,
 140.69 (2Ph)

Element analysis $\text{C}_{18}\text{H}_{21}\text{NO}$

theoretical : C,80.86; H,7.91; N,5.24

25 experimental : C,81.06; H,7.65; N,5.11

High-resolution MS (70eV) m/e theoretical : 267.3649

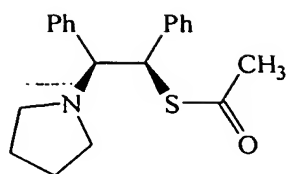
experimental : 267.3688

$[\alpha]_D^{25} = -87.5$ (c = 1, CHCl_3)

melt point: $113.65 \pm 0.45^\circ\text{C}$

30

Step (b): Preparing
 (1R,2S)-1,2-Diphenyl-2-pyrrolidine-1-yl-1-thioacetyl-ethane
 (**7g4b**)



5

Repeat Step (c) of EXAMPLE 6, but replace compound (6g4b) with compound (7g4a). Column chromatography (Silica gel, eluent is n-Hexane:NEt₃ = 100:1) is used to purify the coarse product and a yellow liquid (1.33g) is obtained. The yield is 82% and the other analysis includes:

10 ¹H NMR (400MHz , CDCl₃)

δ 1.74-1.78 (m, 4H, N(CH₂CH₂)₂), 2.28 (s, 3H, COCH₃),
2.50-2.57 (m, 4H, N(CH₂)₂), 3.48 (d, J = 4.8Hz, 1H, NCH), 5.25
(d, J = 5.2Hz, 1H, SCH), 6.88-7.26 (m, 10H, ArH)

¹³C NMR (100MHz , CDCl₃)

15 δ 23.33 (N(CH₂CH₂)₂), 30.83 (COCH₃), 52.62 (N(CH₂)₂), 52.85
(NCH), 74.99 (SCH), 126.88, 127.48, 127.59, 128.88, 129.00,
138.64, 140.33 (2Ph), 196.58 (S_COCH₃)

Element analysis C₂₀H₂₃NOS

theoretical : C, 73.81 ; H, 7.12 ; N, 4.30

20 experimental : C, 73.55 ; H, 7.26 ; N, 4.38

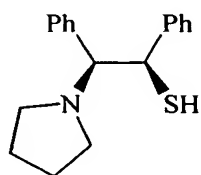
High-resolution MS (70eV) m/e theoretical : 325.4737

experimental : 325.4245

[α]_D²⁵ = -32.5 (c = 1, CHCl₃)

25

Step (c): Preparing (1R,2S)-1,2-Diphenyl-2-pyrrolidine-1-yl- ethane-1-thiol
(7g4c)



30

Repeat Step (c) of EXAMPLE 6, but replace compound (6g4b) with compound (7g4b). A slightly-yellow liquid (0.43g) is obtained. The yield is

76%, and the other analysis includes:

^1H NMR (400MHz , CDCl_3)

5 δ 1.72-1.79 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.29(s, 1H, SH), 2.45-2.51 (m, 2H, NCH_2), 2.55-2.61 (m, 2H, NCH_2), 3.46 (d, $J = 5.6\text{Hz}$, 1H, NCH), 4.70 (d, $J = 5.2\text{Hz}$, 1H, CHSH), 6.96-7.36 (m, 10H, ArH)

^{13}C NMR (100MHz , CDCl_3)

10 δ 23.47 ($\text{N}(\text{CH}_2\text{CH}_2)_2$), 48.60 (NCH), 52.30($\text{N}(\text{CH}_2)_2$), 75.70 (CHSH), 127.05, 127.09, 127.35, 127.72, 128.63, 129.79, 137.40, 140.85 (2Ph)

Element analysis $\text{C}_{18}\text{H}_{21}\text{NS}$

theoretical : C,76.28; H,7.47; N,4.94

experimental: : C,76.06; H,7.28; N,5.23

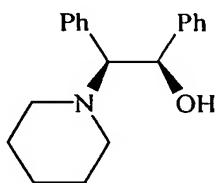
High-resolution MS (70eV) m/e theoretical : 283.4369

15 experimental : 283.4348

$[\alpha]_D^{25} = -162.0$ ($c = 1$, CHCl_3)

EXAMPLE 9: Preparation of (1R,2S)-1,2-Diphenyl-2-piperidin-1-yl-ethanethiol (7g5c)

20 Step (a): Preparing (1R,2S)-1,2-Diphenyl-2-piperidin-1-yl-ethanol (7g5a)



25

Repeat Step (a) of EXAMPLE 6, but replace (1R,2S)-2-amino-1-phenyl- 3-methyl-butanol with (1R,2S)-2-amino-1,2-diphenyl-ethanol, and replace 1,4-dibromobutane with 1,5-dibromopentane. Column chromatography (Silica gel 50g, eluent is n-Hexane:EtOAc = 5:1) is used to purify the coarse product and a white solid (1.28g) is obtained. The yield is 91% and the other analysis includes:

30

^1H NMR (400MHz, CDCl_3)

δ 1.45-1.49 (m, 2H, $((\text{CH}_2)_2\text{CH}_2(\text{CH}_2)_2)$), 1.55-1.62 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.47-2.55 (m, 2H, NCH_2), 2.62 (br, 2H, NCH_2), 3.38

48.78 (NCH) 50.71 (N(CH₂)₂), 73.28 (SCH), 126.67, 127.32, 127.59, 127.81, 128.25, 128.72, 136.03, 141.72 (2Ph)

Element analysis C₂₁H₂₅NO S

theoretical: C, 74.29; H, 7.42; N, 4.13; O, 4.71; S 9.45

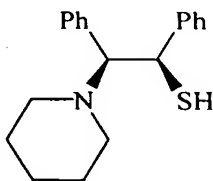
5 experimental: C, 74.19; H, 7.10; N, 4.49; O, 4.52; S 9.70

high-resolution MS (70eV) m/e theoretical: 339.5005

experimental: 339.5436

Step (c): Preparing (1R,2S)-1,2-Diphenyl-2-piperidin-1-yl-ethanethiol (**7g5c**)

10



15 Repeat Step (c) of EXAMPLE 1, but compound (**6g4b**) is replaced with compound (**7g5b**). A transparent liquid (0.505g) is obtained. The yield is 85% and the other analysis includes:

¹H NMR (400MHz , CDCl₃)

20 δ 1.16-1.29 (m, 6H, (CH₂(CH₂CH₂)₂N), 2.01 (SH), 2.18(br, 2H, CH₂(CH₂CH₂)₂N), 2.34 (br, 2H, CH₂(CH₂CH₂)₂N), 3.78 (d, J = 4.8Hz, 1H, NCH), 4.68 (d, J = 4Hz, 1H, SCH), 7.14-7.30 (m, 10H, ArH)

¹³C NMR (100MHz , CDCl₃)

25 δ 24.42 ((CH₂)₂CH₂(CH₂)₂), 26.12 (N(CH₂CH₂)₂), 44.75(NCH) 50.86 (N(CH₂)₂), 76.36 (SCH), 126.84, 127.32, 127.61, 127.89, 128.03, 129.22, 135.75, 142.03 (2Ph)

Element analysis C₁₈H₂₁NS

theoretical: C, 76.72; H, 7.79; N, 4.71; S, 10.78

experimental: C, 76.85; H, 7.83; N, 4.75; S, 10.82

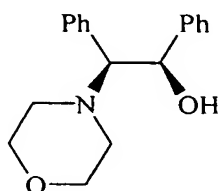
30 High-resolution MS (70eV) m/e theoretical: 297.1551

experimental: 298.0035

[α]_D²⁵ = -122.0 (c = 1, CHCl₃)

EXAMPLE 10: Preparation of
(1*R*,2*S*)-1,2-Diphenyl-2-morpholin-4-yl-ethane-1-thiol
(7g6c)

Step (a): preparing (1*R*,2*S*)-1,2-Diphenyl-2-morpholin-4-yl-ethanol (7g6a)



Repeat Step (a) of EXAMPLE 6, but replace (1*R*,2*S*)-2-amino-1-phenyl-3-methyl-butanol with (1*R*,2*S*)-2-amino-1,2-diphenylethanol, and replace 1,4-dibromobutane with (BrC₂H₄)₂O. Column chromatography (Silica gel 50g, eluent is n-Hexane:EtOAc = 4:1) is used to purify the coarse product and a white solid (1.34g) is obtained. The yield is 95% and the other analysis includes:

¹H NMR (400MHz, CDCl₃)

δ 2.51-2.56 (m, 2H, N(CH₂)₂), 2.66 (br, 2H, N(CH₂)₂), 3.30 (s, 1H, OH), 3.36 (d, J = 4.0Hz, 1H, NCH), 3.70-3.76 (m, 4H, O(CH₂)₂), 5.33 (d, J = 4.0Hz, 1H, CHOH), 6.94-7.26 (m, 10H, ArH)

¹³C NMR (100MHz, CDCl₃)

δ 51.96 (N(CH₂)₂), 67.11 (O(CH₂)₂), 71.18 (NCH), 76.44 (CHOH), 126.11, 126.87, 127.40, 127.56, 127.60, 129.54, 135.56, 140.81 (2Ph)

IR ν_{max} (cm⁻¹) 3127 (OH)

Element analysis C₁₈H₂₁NO₂

theoretical: C,76.33; H,7.46; N,4.93; O,11.28

experimental: C,76.38; H,7.36; N,4.90; O,11.36

High-resolution MS (70eV) m/e theoretical: 283.1573

experimental: 283.1570

[α]_D²⁵ = -140.7 (c = 1.4, CHCl₃)

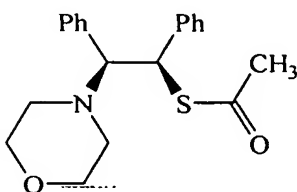
melting point: 123-125°C

Step

(b):

Preparing

(1R,2S)-1,2-Diphenyl-2-morpholin-4-yl-1-thioacetyl-ethane
(7g6b)



Repeat Step (b) of EXAMPLE 6, but replace compound (6g4a) with compound (7g6a). Column chromatography (Silica gel 70g, eluent is n-Hexane:NEt₃ = 100:1) is used to purify the coarse product and an orange solid (1.57g) is obtained. The yield is 92% and the other analysis includes:

¹H NMR (400MHz, CDCl₃)

δ 2.20 (s, 3H, COCH₃), 2.31-2.35 (m, 2H, N(CH₂)₂), 2.46 (m, 2H, N(CH₂)₂), 3.51(m, 4H, O(CH₂)₂), 3.72 (d, J = 8.8Hz, 1H, NCH), , 5.28 (d, J = 8.4Hz, 1H, SCH), 7.05-7.27 (m, 10H, ArH)

¹³C NMR (100MHz, CDCl₃)

δ 30.58(COCH₃), 48.88(NCH), 50.49 (N(CH₂)₂), 66.95(O(CH₂)₂), 73.63(SCH), 126.93, 127.72, 127.78, 127.86, 128.43, 128.94, 135.88, 140.87 (2Ph)

Element analysis C₂₀H₂₃NO₂S

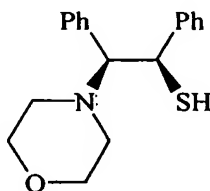
theoretical: C,70.35; H,6.79; N,4.10; O,9.37; S9.39

experimental: C,70.85; H,6.14; N,4.69; O,6.17; S9.15

High-resolution MS (70eV) m/e theoretical: 341.4727

experimental: 341.4794

Step (c): Preparing (1R,2S)-1,2-Diphenyl-2-morpholin-4-yl-ethane-1-thiol (7g6c)



Repeat Step (c) of EXAMPLE 6, but replace compound (6g4b) with

solution. The solution is then extracted with acetyl acetate (20 mL), wherein the organic layer is collected and dehydrated with anhydrous MgSO_4 , and then the mixture is filtered. The filtrate is concentrated by reducing pressure through an air pump to obtain crude product. The crude product is purified by column chromatography (Silica gel, eluent is n-Hexane: EtOAc = 10: 1).

HPLC (high-pressure liquid chromatography) with Daicel Chiralcel OD Column is provided for determining enantiomeric excess (e.e.) of the product, wherein the eluent is n-hexane:i-propanol = 98.0:2.0, flow rate is 1.5 ml/min. In the above addition reaction of ZnEt_2 and various aldehyde, peaks of products are present at different time, as indicated in Table 3. The enantiomeric excess (e.e.) can be determined according to the following equation:

$$\text{e.e.(\%)} = \frac{|S-R|}{S+R} \times 100\%$$

wherein (S+R) in denominator is the product obtained without adding chiral ligands of the present invention;

S or R in numerator is the product obtained by adding chiral ligands of the present invention.

Table 2

EXAMPLE	Ligand	N _{lig} (meq)	S/C	N _{ZE} (meq)	Solvent	t _{rxn} (h)	T _{rxn} (°C)	e.e. (%)
1	6b4c	0.05	20	1.2	Toluene	12	-20	96.5 R
2	2f4c	0.05	20	1.2	Toluene	12	-20	95.7 R
3	6c4c	0.05	20	1.2	Toluene	12	-20	94.2 R
4	3f4c	0.05	20	1.2	Toluene	12	-20	93.2 R
5	6f4c	0.05	20	1.2	Toluene	12	-20	99.6 R
		0.05	20	1.2	Toluene	6	rt	98.5 R
		0.05	20	1.2	Toluene	12	0	99.3 R
		0.05	20	1.2	Toluene	12	-20	99.6 R
		0.05	20	1.2	Hexane	12	-20	99.2 R
		0.05	20	1.2	T/THF	12	-20	92.1 R
		0.05	20	1.2	T/CH ₂ Cl ₂	12	-20	99.5 R
		0.05	20	2	Toluene	12	-20	99.6 R
		0.05	20	3	Toluene	12	-20	99.5 R

(continued)

EXAMPLE	Ligand	Nlig (meq)	S/C	NZE (meq)	Solvent	txn (h)	Trxn (°C)	e.e. (%)
5	6f4c	0.05	20	4	Toluene	12	-20	99.5 R
		0.05	20	5	Toluene	12	-20	99.5 R
		0.05	20	1.2	Toluene	12	-40	99.7 R
		0.05	20	1.2	Toluene	24	-78	90.2 R
		0.5	2	1.2	Toluene	12	-20	99.6 R
		0.2	5	1.2	Toluene	12	-20	99.6 R
		0.05	20	1.2	Toluene	12	-20	99.6 R
		0.001	1000	1.2	Toluene	12	-20	99.2 R
		0.0005	2000	1.2	Toluene	12	-20	98.5 R
		0.0001	10000	1.2	Toluene	12	-20	96.5 R
6	6g4c	0.05	20	1.2	Toluene	6	rt	98.3 R
		0.05	20	1.2	Toluene	12	0	99.3 R
		0.05	20	1.2	Toluene	12	-20	99.5 R
		0.05	20	1.2	Toluene	12	-40	99.6 R
		0.05	20	1.2	Toluene	24	-78	88.2 R
7	6g5c	0.05	20	1.2	Toluene	12	rt	99.0 R
		0.05	20	1.2	Toluene	12	0	99.0 R
		0.05	20	1.2	Toluene	12	-20	99.6 R
		0.01	100	1.2	Toluene	12	-20	99.0 R
		0.001	1000	1.2	Toluene	12	-20	98.1 R
		0.05	20	1.2	Toluene	12	-40	99.6 R
		0.05	20	1.2	Toluene	12	-78	93.7 R
8	7g4c	0.1	10	5	Toluene	12	-20	99.3 R
		0.1	10	4	Toluene	12	-20	99.5 R
		0.1	10	3.7	Toluene	12	-20	99.5 R
		0.1	10	3	Toluene	12	-20	99.4 R
		0.1	10	2	Toluene	12	-20	99.3 R
		0.1	10	1.2	Toluene	12	-20	99.3 R
		0.05	20	1.2	Toluene	6	rt	99.1 R
		0.05	20	1.2	Toluene	9	0	99.2 R
		0.05	20	1.2	Toluene	12	-20	99.3 R
		0.05	20	1.2	Toluene	12	-40	99.5 R
		0.05	20	1.2	Toluene	24	-78	94.2 R
		0.0002	5000	3.7	Toluene	12	-20	99.0 R
		0.0005	2000	3.7	Toluene	12	-20	99.1 R
		0.001	1000	3.7	Toluene	12	-20	99.2 R

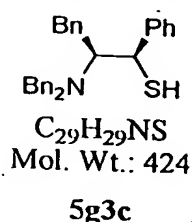
(continued)

EXAMPLE	Ligand	Nlig (meq)	S/C	NZE (meq)	Solvent	txn (h)	Trxn (°C)	e.e. (%)
8	7g4c	0.003	333	3.7	Toluene	12	-20	99.3 R
		0.006	167	3.7	Toluene	12	-20	99.3 R
		0.01	100	3.7	Toluene	12	-20	99.3 R
		0.02	50	3.7	Toluene	12	-20	99.4 R
		0.05	20	3.7	Toluene	12	-20	99.4 R
		0.1	10	3.7	Toluene	12	-20	99.5 R
		0.2	5	3.7	Toluene	12	-20	99.5 R
		0.4	3	3.7	Toluene	12	-20	98.8 R
9	7g5c	0.1	10	3.7	Toluene	12	-20	99.7 R
		0.05	20	2	Toluene	12	0	99.7 R
10	7g6c	0.1	10	3.7	Toluene	12	-20	99.5 R

In Table 2, S/C is an equivalence ratio of benzaldehyde (substrate, 1.0 mmol) to the chiral ligand. As shown in Table 2, the chiral ligands of the present invention exhibit superior enantioselectivity in the asymmetric of benzaldehyde and diethyl zinc, even as S/C are very high. For example, when compounds (6f4c), (6g5c) and (7g4c) obtained from EXAMPLEs 5, 7 and 8 are applied at S/C as high as 1,000, enantiomeric excess are more than 98%. Therefore, aminothiols in the present invention are indeed very economic for applying the above asymmetric reactions to industries.

Table 3 list more aminothiol compounds with various ligands and application results thereof in varied reaction conditions. These aminothiol compounds can be produced through similar procedures of above EXAMPLEs by supplying proper reactants having respective ligands. Therefore, detailed description is omitted in the specification.

In Table 3, Compound (5g3c) has the following formula.



The related analysis of Compound (5g3c) include:
 1H NMR (400MHz, $CDCl_3$)

δ 3.04-3.22(m, 2H, PhCH₂), 3.503.60 (m, 1H, CNH), 3.60 (s, 4H, PhCH₂N), 4.37 (t, J=4.0Hz, 1H, PhCHS), 6.81-7.41 (m, 20H, ArH)
¹³C NMR (100MHz, CDCl₃)

5 δ 24.68, 26.53, 46.06, 51.41, 72.86, 125.83, 126.81, 127.94, 128.10, 128.14, 129.31, 140.85, 143.663.

Element analysis C₂₉H₂₉NS

Table 3

Ligand	N _{lig} (meq)	S/C	N _{ZE} (meq)	Solvent	t _{rxn} (h)	T _{rxn} (°C)	e.e. (%)
2g5c	0.05	20	2	Hexane	12	0	100.0 R
4g5c	0.05	20	1.2	Toluene	12	rt	91.0 R
	0.05	20	1.2	Toluene	12	0	97.9 R
	0.0005	2000	1.2	Toluene	12	-20	97.7 R
	0.0001	10000	1.2	Toluene	12	-20	98.1 R
	0.005	200	1.2	Toluene	12	-20	98.1 R
	0.001	1000	1.2	Toluene	12	-20	98.1 R
	0.05	20	1.2	Toluene	12	-20	98.9 R
	0.1	10	1.2	Toluene	12	-20	98.9 R
	0.2	5	1.2	Toluene	12	-20	98.8 R
	0.05	20	1.2	Toluene	12	-40	99.3 R
5g2c	0.05	20	1.2	Toluene	12	rt	96.9 R
5g3c	0.05	20	1.2	Toluene	12	0	93.5 R
5g4c	0.05	20	1.2	Toluene	12	0	98.9 R
5g5c	0.05	20	5	Toluene	12	0	99.1 R
	0.05	20	4	Toluene	12	0	99.4 R
	0.05	20	3	Toluene	12	0	99.4 R
	0.05	20	2	Toluene	12	0	99.3 R
	0.05	20	1.2	Toluene	12	0	99.3 R

(continued)

Ligand	N _{lig} (meq)	S/C	N _{ZE} (meq)	Solvent	t _{rxn} (h)	T _{rxn} (°C)	e.e. (%)
5g5c	0.05	20	1.1	Toluene	12	0	99.3 R
	0.05	20	1.2	Hexane	12	0	99.1 R
	0.05	20	1.2	T/CH ₂ Cl ₂	12	0	99.1 R
	0.05	20	1.2	T/THF	12	0	72.0 R
	0.0001	10000	1.2	Toluene	12	0	98.1 R
	0.0002	5000	1.2	Toluene	12	0	98.9 R
	0.0005	2000	1.2	Toluene	12	0	99.0 R
	0.001	1000	1.2	Toluene	12	0	99.1 R
	0.002	500	1.2	Toluene	12	0	99.1 R
	0.005	200	1.2	Toluene	12	0	99.2 R
	0.01	100	1.2	Toluene	12	0	99.3 R
	0.02	50	1.2	Toluene	12	0	99.3 R
	0.05	20	1.2	Toluene	12	0	99.3 R
	0.1	10	1.2	Toluene	12	0	99.4 R
	0.2	5	1.2	Toluene	12	0	99.4 R
	0.5	2	1.2	Toluene	12	0	99.4 R
	1	1	1.2	Toluene	12	0	99.0 R
	0.05	20	1.2	Toluene	3	rt	98.1 R
	0.05	20	1.2	Toluene	12	0	99.3 R
	0.05	20	1.2	Toluene	18	-20	99.4 R
	0.05	20	1.2	Toluene	24	-40	99.4 R
	0.05	20	1.2	Toluene	48	-78	87.9 R
	0.05	20	1.2	Toluene	0.5	rt	97.8 R
	0.05	20	1.2	Toluene	1	rt	98.1 R
	0.05	20	1.2	Toluene	1.5	rt	98.1 R

(continued)

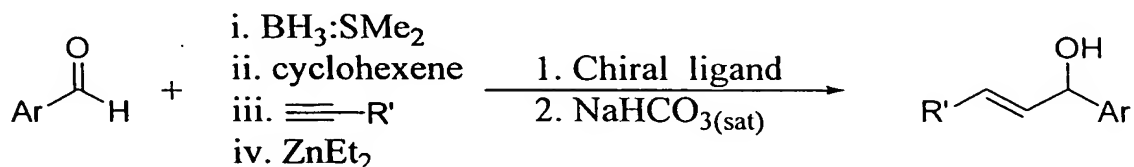
Ligand	N _{lig} (meq)	S/C	N _{ZE} (meq)	Solvent	t _{rxn} (h)	T _{rxn} (°C)	e.e. (%)
5g5c	0.05	20	1.2	Toluene	3	rt	98.1 R
	0.05	20	1.2	Toluene	6	rt	98.1 R
5g6c	0.05	20	1.2	Toluene	12	0	98.2 R
6g1c	0.05	20	1.2	Toluene	12	-20	97.7 R
6g2c	0.05	20	1.2	Toluene	12	-20	99.4 R
6g6c	0.05	20	1.2	Toluene	12	0	99.1 R
	0.05	20	1.2	Toluene	12	-20	99.4 R

As shown in Table 3, the aminothiols compounds of the present invention indeed perform excellent catalysts to obtain high enantiomeric excess in the asymmetric addition reaction of benzaldehyde and diethyl zinc.

Similarly, the aminothiols compounds of the present invention can be provided as chiral ligands to react with other organic metals, for example, Cu, to form organometal complexes. These complexes can also react with carbonyl such as aldehyde, to produce alcohol in the asymmetric addition reactions.

【Application Mode 2】

The aminothiols compounds of the present invention also show superior effect in catalyzing an addition reaction as follows:



In this reaction, butyl acetylene (or hexyl acetylene), diethylzinc (ZnEt₂) and aldehyde are reacted to produce allyl alcohol in existence of chiral ligands of the present invention. Table 4 lists conditions and results of the reaction catalyzed with different ligands including Compound (6g5c) obtained in Example 7, Compound (7g5c) obtained in Example 9,

Compound (7g6c) obtained in Example 10 and Compound (6f5c).

Table 4

Ligand	Ar	R'	Mole % of ligand	T _{rxn} (°C)	N _{ZE} (eq)	t _{rxn} (h)	Conversion (%)	Yield (%)	e.e (%)
6f5c	Ph	C ₄ H ₉	5(T)	-10	2	15	100	89	91.3(R)
	Ph	C ₄ H ₉	5(T)	-20	2	15	100	94	99.0(R)
	Ph	C ₄ H ₉	5(T)	-20	2	15	100	94	98.3(R)
	Ph	C ₄ H ₉	1(T)	-30	2	15	100	90	94.3(R)
	Ph	C ₄ H ₉	2(T)	-30	2	15	100	92	94.5(R)
	Ph	C ₄ H ₉	5(T)	-30	2	15	100	94	98.2(R)
	Ph	C ₆ H ₁₃	2(T)	-30	2	15	100	65	99.0(R)
	4-OMe-Ph	C ₆ H ₁₃	2(T)	-30	2	15	100	90	98.1(R)
	2-Cl-Ph	C ₆ H ₁₃	2(T)	-30	2	15	100	86	92.6(R)
	Ph	C ₆ H ₁₃	2(H)	-30	2	15	100	80	99.0(R)
	Ph	C ₄ H ₉	5(T)	-30	2	15	100	94	98.2(R)
	2-Cl-Ph	C ₄ H ₉	5(T)	-30	2	15	100	-	98.1(R)
	Ph	C ₆ H ₁₃	5(T)	-30	2	15	100	-	99.4(R)
	Ph	C ₄ H ₉	5(T)	-40	2	15	100	94	98.3(R)
	Ph	C ₄ H ₉	15(T)	-30	2	15	100	-	99.5(R)
6g5c	Ph	C ₄ H ₉	5(T)	-30	2	15	100	92	96.1(R)
	Ph	C ₆ H ₁₃	2(T)	-30	2	15	100	92	98.6(R)
7g5c	Ph	C ₄ H ₉	5(T)	-30	2	15	100	91	95.6(S)
	Ph	C ₄ H ₉	5(T)	-30	2	15	100	93	97.0(R)
	Ph	C ₆ H ₁₃	2(T)	-30	2	15	100	93	98.4(R)
	Ph	C ₆ H ₁₃	5(T)	-30	2	15	100	68	98.3(R)
7g6c	Ph	C ₄ H ₉	5(T)	-30	2	15	100	95	97.3(R)

5 In Application Mode 2, ZnEt₂ and aldehyde are respectively added by syringe pump over 20 minutes. T and H in the column (mole % of ligand) are the solvents toluene and hexane. Detailed procedures may be referred to Wolfgang Oppolzer et al. (J. Org. Chem. 2001, 66, 4766-4770) and Brase S. et al. (Org. Lett. 2001, 3, 4119). Enantiometric access is determined with

HPLC (Chiralcel OD-H column, flow rate 0.7ml/min, 3% isopropanol).

It should be noticed that the above embodiments are only used for explaining the present invention, but not limiting the scope.